



Rice, C. M., & Scolding, N. J. (2019). The diagnosis of primary central nervous system vasculitis. *Practical Neurology*.  
<https://doi.org/10.1136/practneurol-2018-002002>

Peer reviewed version

Link to published version (if available):  
[10.1136/practneurol-2018-002002](https://doi.org/10.1136/practneurol-2018-002002)

[Link to publication record in Explore Bristol Research](#)  
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via BMJ Publishing Group at <https://pn.bmj.com/content/early/2019/10/24/practneurol-2018-002002> . Please refer to any applicable terms of use of the publisher.

## University of Bristol - Explore Bristol Research

### General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:  
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

# The diagnosis of Primary Central Nervous System Vasculitis

Claire Rice and Neil Scolding

## Abstract

The diagnosis of Primary Central Nervous System Vasculitis (PCNSV) ~~remains-is commonly very difficult~~challenging in the majority of cases. There are neither specific clinical features nor a classical clinical course, ~~and~~. There are no blood or imaging investigations that can confirm the diagnosis—~~though these play a vital role particularly in excluding other disorders~~. Contrast catheter cerebral angiography is ~~universally accepted to be~~ neither specific nor sensitive, yet remains-still underpins the ~~mainstay of~~ diagnosis in many published studies ~~There have been few if any changes in treatment in the past four decades, and no treatment trials have been conducted~~. Here we describe an approach to the diagnosis of PCNSV, ~~we~~ emphasise the importance of obtaining tissue ~~as part of this approach~~, and ~~we~~ present for discussion a new, binary set of diagnostic criteria, dividing ~~putative~~ cases only into 'definite' PCNSV, where tissue proof is available, and 'possible,' where it is not. We hope that ~~the details of~~ these criteria will be modified and significantly improved by discussion amongst ~~others with expertise of in PCNSV the disorder; and-but~~ that these (improved) criteria may then be adopted and used as the basis for future prospective studies of the clinical features, ~~and~~ diagnosis ~~and treatment~~ of this difficult and dangerous disorder, including-and in particular for coordinated multi-centre therapeutic trials.

## Introduction.

Cerebral vasculitis is a descriptive term rather than a specific disease, referring to inflammation within the wall of CNS blood vessels associated with destructive changes, occlusion and infarction<sup>1,2</sup>. 'Secondary' CNS vasculitis is where the CNS becomes involved in a systemic vasculitic illness, including but not limited to the systemic vasculitides (such as microscopic polyarteritis, or granulomatosis with polyangiitis, formerly known eponymously as Wegener's granulomatosis; see Table One). Conversely, in 'primary' or 'isolated' vasculitis or angiitis of the CNS (here we will use the term Primary CNS Vasculitis, PCNSV), there is little or no overt generalised inflammation. All forms of cerebral vasculitis are relatively rare, but all are serious, and potentially life-threatening.

Secondary CNS vasculitis can be a relatively straightforward diagnosis, often clearly suggested by clinically eloquent concurrent or recent disease in more accessible organs – lungs, kidneys, joints, skin etc. However, in the case of CNS features occurring when a systemic vasculitic illness has been long present,

the occasionally complex question can arise of distinguishing secondary CNS involvement of vasculitis from iatrogenic immunosuppressant-related opportunistic infection.

Making a diagnosis of primary CNS vasculitis is, commonly, far more challenging, for several reasons. Its rarity means few neurology units have extensive clinical experience of the disorder<sup>3</sup>. There is no diagnostically distinct clinical picture<sup>4-10</sup>. There are no fail-safe indirect diagnostic tests (including contrast/digital subtraction angiography; see below). The brain, and even more the spinal cord, is relatively inaccessible and potentially hazardous to biopsy.

But not least amongst these difficulties of diagnosis is that the criteria upon which a clinical diagnosis of PCNSV can be made have not been firmly established or uniformly accepted<sup>9,11</sup>. There is no real consensus on defining the disease – criteria for allowing a diagnosis based on angiography without histology are very commonly utilized in published studies and reports<sup>9,12-20</sup>. Other authors do recommend relying on histology<sup>10,11,20-23</sup>. Such variability of patient inclusion criteria naturally renders interpretation difficult and has restricted progress in optimizing treatment. We suggest it would be valuable to divide patients into just two diagnostic groups according to the certainty of diagnosis. Here, in addition to refining our previously suggested investigational approach to suspected CNS vasculitis<sup>6</sup>, we propose simple draft diagnostic criteria delineating ‘definite’ and ‘possible’ PCNSV. We hope that these criteria can be modified by consensus and improved in the future; they could then act as the foundation for more detailed prospective analyses, and hopefully facilitate the design of future therapeutic trials.

### **Clinical features and investigation**

There is no pathognomic clinical picture in PCNSV. Innumerable neurological features occur, depending on the site of the vasculature affected, with a clinical course that may be acute or subacute, more chronically progressive, or relapsing and remitting<sup>4,5,9,21,24,25</sup>. Headache is common, as are other non-specific or non-focal features such as encephalopathy, cognitive change, and generalized seizures; but focal neurological abnormalities are also common, including hemispheric, brainstem or spinal deficits, movement disorders and optic and other cranial neuropathies. Relatively non-specific systemic features of inflammatory disease, such as fever, night sweats, livedo reticularis, and oligoarthropathy may also be revealed if specifically sought.

To aid the initial clinical suspicion and recognition of PCNSV, three distinct presentations encompassing this wide diversity of clinical features were previously delineated<sup>6,26</sup> :-

- an acute or subacute encephalopathy, commonly presenting as an acute confusional state, progressing to drowsiness and coma;
- a picture that superficially resembles multiple sclerosis but with atypical features (‘MS-plus’ or ‘pseudo-MS’) – a relapsing-remitting course including, for example, optic neuropathy and brain stem episodes, but also other features less common in multiple sclerosis, such as seizures, severe and persisting headaches, encephalopathic episodes, or hemispheric stroke-like episodes; or

- intracranial mass lesion[s] with headache, drowsiness, focal signs and often raised intracranial pressure.

These are also, of course, non-specific, and may be seen in many neurological disorders, but unless an alternative explanation is immediately obvious, their occurrence should lead to PCNSV at least being included in the differential diagnosis.

As with the clinical features, so for investigations: there are no biochemical, immunological or serological or imaging investigations that are diagnostic of PCNSV. Non-specific changes are common – a normochromic anaemia, and raised plasma viscosity, for example. In a highly informative systematic review of published cases, brain MRI was reported to be abnormal in 93.3% of patients (i.e., it can be normal), and CSF abnormal in 74.4%. In both cases the abnormalities again were wholly non-specific<sup>27</sup>. Efforts to develop specific MRI-based approaches for demonstrating cerebral vasculitis continue, including vessel wall imaging<sup>28</sup>, but will require rigorous MR-neuropathological correlation before they can usefully be applied.

Therefore, rather than ‘confirming’ PCNSV, the main role of blood tests, CT of chest, abdomen and pelvis, CSF examination and MRI scanning is to help exclude alternative inflammatory or autoimmune, infective, malignant or other disorders, not uncommonly identifying clinically occult systemic involvement and accessible targets for tissue biopsy. Ocular examination, including slit-lamp ophthalmoscopy<sup>29</sup>, together with whole-body CT-PET scanning, can play a similar important role.

It might be predicted that a disease of blood vessels might be diagnosed by imaging the affected area’s vasculature, and cerebral catheter contrast angiography/digital subtraction, CT- and/or MR-angiography can indeed show abnormalities. Segmental (often multifocal) narrowing with areas of localized dilatation or beading may be seen; single stenotic areas in multiple vessels are said to be more frequent in PCNSV than multiple stenotic areas along a single vessel. Formal contrast/digital subtraction angiography continues to be associated with a small but significant risk of stroke and, with improvements in MR resolution, the likelihood that formal contrast/digital subtraction angiography will add diagnostic information above that provided by MR/CT angiography is decreasing. However, precise determination of sensitivity and specificity of MR/CT angiography is currently unknown due to lack of histological confirmation in published studies<sup>30,31</sup> – although unlikely to be greater than that of formal contrast/digital subtraction angiography. [CR1]

As mentioned above, many published studies have depended on catheter angiography in their diagnostic confirmation (or exclusion) of PCNSV. However, it has been clear since at least the early 1970s that similar, so-called ‘vasculitic’ changes may alternatively be seen in atherosclerotic disease, as a reactive change following subarachnoid haemorrhage, in migraine, trauma, hypertension, infections, radiation vasculopathy and following illicit drug use<sup>22,32</sup>. Later, careful studies using histopathological evidence show catheter angiography to have both sensitivity and specificity of around 25–35%.<sup>9,25,27,33–36</sup> (CT-based or MR angiography is even less sensitive.<sup>37,38</sup>) A normal angiogram therefore cannot exclude PCNSV, while a large number of alternative inflammatory, metabolic, malignant or other vasculopathies mimic PCNSV on angiography – ‘vasculitic’ changes in fact imply no more than a potential vasculopathy still requiring

diagnosis. Reversible Cerebral Vasoconstriction Syndrome (RCVS) can represent a particularly difficult diagnostic alternative, though an extremely careful and authoritative comparative study has valuably highlighted the key clinical and investigational differences.<sup>39</sup> **MRI based vessel wall imaging may help.**<sup>40</sup>

## Cerebral biopsy

Given the lack of alternative methods of achieving a secure diagnosis, it would appear axiomatic that CNS tissue biopsy is required to make a diagnosis of PCNSV. There is, however, a natural reluctance to undertake such an invasive procedure, the more so should a particularly eloquent site be the only target – dominant temporo-parietal lesions, for example, or those in the brain stem or spinal cord. In addition to the potential risks is the question of the imperfect sensitivity, those occasions when neuropathological examination shows only ‘non-specific change’ or ‘end-stage tissue damage infarction/gliosis’.

In our view, a number of considerations, combined with a growing body of observational research evidence, very strongly tilt the balance in favour of biopsy.

First, several studies attest to the relative safety of brain biopsy. The qualifier ‘relative’ is crucial, given the life-threatening nature of the disease in question, of some of the alternative diagnostic possibilities, and indeed of treatments that may be required if CNS vasculitis is present. In one retrospective study of some 61 patients biopsied for suspected CNS vasculitis, there were no mortalities and not a single patient suffered any permanent ill-effects from the procedure.<sup>33</sup> In our study of 56 brain biopsies in cryptogenic neurological disease, there were no deaths or permanent deficits<sup>41</sup>. In a much larger more general brain biopsy series, the safety of stereotactic biopsy in over 7000 procedures was assessed: the mortality rate was less than 1%, and the morbidity rate was 3.5% though only few of these had permanent disability<sup>42</sup>. (In fact there is some evidence that the mortality and morbidity in biopsying suspected malignancy is higher than with cryptogenic neurological disease: in a biopsy meta-analysis restricted to 831 cases of the latter, procedure-related mortality was zero.<sup>43</sup>) It is also becoming clear that even brain stem and spinal cord biopsies are less hazardous than previously thought<sup>44</sup>. Various authorities have presented data indicating that the risks of immunosuppressive treatments are greater than those of biopsy<sup>13,45</sup>.

Secondly, we now know more of the diagnostic yield and clinical utility of biopsy. The sensitivity is considered to lie in the range 50-70%.<sup>9,25,33,41</sup> Perhaps more importantly, some 75% of patients receive a clear diagnosis – of vasculitis or some other specific pathology, following biopsy.<sup>33,41,45</sup> Not uncommonly, the alternative, unsuspected diagnosis to emerge from biopsy is infective – 10 out of 61 biopsies in one series<sup>33</sup>, emphasizing the importance of not ‘assuming’ vasculitis and treating with immunosuppressants. A very recent meta-analysis suggested no significant difference between frame-based and frameless biopsy in terms of diagnostic yield, morbidity, and mortality.<sup>46</sup>

Finally, as mentioned in the first sentence, cerebral vasculitis is a descriptive term, not a disease, and it has always been anticipated that the term ‘PCNSV’ would comprise a spectrum of specific disorders. These are now slowly being dissected and described.<sup>47-49</sup> Aβ-related Angiitis (ABRA) is one such disorder, likely a sub-type of cerebral amyloid angiopathy (CAA) wherein intramural amyloid deposits have triggered an anti-amyloid inflammatory reaction and so vasculitic change. Clearly, only biopsy can

distinguish ABRA from other forms of PCNSV (and from Cerebral Amyloid Angiopathy-Related Inflammation, in which peri-vascular inflammation is apparent in the context of CAA – again perhaps triggered by amyloid deposition – but without vasculitis)); similarly, only biopsy can identify the other recognized forms of the condition.<sup>47-49</sup> In addition, though plainly not an argument that should sway the decision in any specific individual case, it is only by looking at tissue that further specific entities ~~we~~ will come to ~~understand the likely collection of diseases that underlie PCNSV,~~<sup>47-49</sup> ~~and so help acquire the basic knowledge required to develop specific treatments~~be described.

## Treatment

The treatment of PCNSV has no direct clinical trial evidence base, and recommendations have changed little if at all in several decades. Cyclophosphamide and steroids remain the core of treatment<sup>6,10,22,50</sup>, the former yielding to less toxic immunosuppressants such as azathioprine or methotrexate after an induction period generally of 10-12 weeks<sup>51</sup> – this approach based principally on evidence from renal and/or rheumatological trials where the diagnosis can be robustly determined either serologically or following tissue biopsy. Mycophenolate – at least in systemic vasculitis – appears less effective in maintaining remission than azathioprine or methotrexate<sup>52</sup>. There are reports of the potential efficacy of rituximab<sup>53</sup>, but again these are often based on cases lacking histopathological verification, and so are open to question.

## Proposed diagnostic criteria for PCNSV

It could be asserted that neither our understanding of the cause[s] of PCNSV, nor approaches to diagnosis, nor treatment recommendations, have advanced significantly over the past two or three decades or more, perhaps with the exception of the recognition of distinct pathological sub-types. We continue to have no randomized treatment trials to provide evidence-based treatment – some of the earliest studies of the disease over thirty years ago recommended cyclophosphamide for definite disease, and this remains the treatment of choice, based almost entirely on evidence from studies of vasculitis in other tissues. PCNSV is an uncommon disorder, but progress in relation to many other diseases of comparable rarity has been far greater.

A major contributing factor to this stasis has been the enormous variation in diagnostic approach – it has been estimated that 75% of published cases lack histopathological proof<sup>54</sup>. Given the consistent range of disorders revealed by published biopsy-based studies of cases considered likely cerebral vasculitis, and with this, the commensurate low yield of vasculitis (in one study of brain biopsies performed at one (major) US academic hospital for consideration of CNS vasculitis within an 8-year window, none of the 14 patients with clinical and angiographic features thought to be diagnostic for PACNS had vasculitis on biopsy<sup>55</sup>); and given the extensive range of disorders now clearly known to show angiographic changes of ‘vasculitis’, it is hard to defend the current accepted practice that cases lacking biopsy proof can still be labelled as ‘definite’ diagnoses of PCNSV in published series and studies.

We therefore propose simple, readily applied binary diagnostic criteria (Table 2) – ‘possible’ or ‘definite’ PCNSV. We have no doubt that the details of these criteria can be modified and significantly improved by

others who have experience of the disorder, and indeed we hope they will be. But more than this, we hope that the principle of histopathological proof may ultimately be accepted generally.

Vasculitis confined to the CNS was first fully described 60 years ago by Cravioto and Feigin, who delineated the classical histopathological features of the disorder, definitively describing it as a “diffuse disorder of the central nervous system with some focal accentuation”<sup>2</sup>. However, it was Calabrese and Mallek’s landmark study three decades later that provided a lasting account of the clinical features, summarized the angiographic changes, and emphasised the recommendation for high dose corticosteroids and cytotoxic drugs, specifically cyclophosphamide, in therapy<sup>9</sup>. Calabrese and Mallek defined the disorder as “an acquired clinical disease characterized by CNS dysfunction that remains unexplained following thorough clinical, laboratory, and neurological investigations; appears to be unassociated with systemic illness, and yields evidence by cerebral angiography or biopsy of CNS tissue of vasculitis confined to the CNS.” Working from this definition, they also proposed the first diagnostic criteria for primary angiitis of the CNS: (1) a history or clinical findings of an acquired neurologic deficit, which remained unexplained after a thorough initial basic evaluation; (2) either classic angiographic or histopathologic features of angiitis within the CNS, and (3) no evidence of systemic vasculitis or of any other condition to which the angiographic or pathologic features could be secondary<sup>9</sup>. Ongoing series continue to utilize these criteria, or variations of them, allowing diagnosis to rest on angiography without biopsy<sup>12,13</sup>.

Subsequent studies over the next two decades, however, confirmed that contrast cerebral angiographic changes considered typical and diagnostic of vasculitis were not at all specific to the disorder (Table 3). Furthermore, many cases of confirmed PCNSV were noted to have normal cerebral angiograms. Calabrese himself subsequently confirmed in a direct study that both the diagnostic specificity and the positive predictive value of cerebral angiography in this context were less than 30%<sup>36</sup>. Therefore, so low is the specificity that patients with ‘typical’ vasculitic changes can be said not just possibly to have a disorder other than PCNSV but statistically more likely to have an alternative disorder.<sup>11,27,45,55</sup> Consequently, many authors have stressed the importance of tissue biopsy to confirm the diagnosis, and there have been sporadic proposals of diagnostic criteria that require biopsy proof for a definite diagnosis.<sup>4,6,11,20,56</sup> Powers<sup>11</sup>, for example, asserted that “patients without histologic confirmation should not be included in case reports, case series, or reviews”.

Such proposals have, however, been far from universally accepted. In a highly informative 2017 systematic study of diagnostic test results in PCNSV<sup>27</sup>, the authors identified 701 published PCNSV cases. The diagnosis had been confirmed by biopsy in just 248 of these patients (35.4%). In 99 individuals with vasculitis on biopsy, cerebral angiography was normal. Looking at trends over time, the authors also reported an increasing diagnostic reliance on angiography and decreasing histopathologic testing over the past two decades. They too recommended a ‘definite’ category for diagnosis restricted to those cases where tissue proof confirmation was available. Despite these recommendations, current ongoing studies and even nationwide prospective surveys continue to include patients without histological confirmation.<sup>13</sup>

The draft criteria we propose also require tissue proof for a ‘definite’ categorization. They are more rigorous than perhaps any used in any published study of the disease, but we believe this is absolutely

justified by the range of disorders that mimic PCNSV (particularly angiographically). We propose that there is no 'probable' category, given the low specificity of contrast angiography. Rather, we suggest that all suspected cases lacking histological proof should be described as 'possible', and the role of angiography therefore implicitly restricted to excluding other specific disorders (moya-moya, and fibromuscular dysplasia, for example). These new criteria could be used as the basis for retrospective literature-based studies of the disease and, we hope in particular, for future prospective studies of the clinical features, diagnosis and treatment of this difficult and dangerous disorder.

#### KEY POINTS:-

- in isolated CNS vasculitis, cerebral angiography without histology is NOT diagnostic
- CNS biopsy is diagnostically important and relatively safe
- we propose binary diagnostic criteria, categorizing cases as either "definite" or "possible" – abandoning any 'probable' category



TABLE ONE

Conditions associated with CNS vasculitis

**Idiopathic/isolated/primary cerebral/CNS vasculitis**

[Eale's disease  
Cogan's syndrome]  
Amyloid- $\beta$ -related angiitis

**Secondary CNS vasculitis**

**Systemic vasculitides**

Wegener's granulomatosis  
Churg-Strauss syndrome  
Behçet's disease  
Microscopic polyarteritis nodosa  
Classical PAN  
Small vessel vasculitis [inc. HSP]  
Kawasaki disease  
Giant-cell arteritis  
Takayasu's arteritis

**Connective tissue diseases**

Systemic lupus erythematosus  
Antiphospholipid antibody syndrome  
Rheumatoid arthritis  
Sjögren's syndrome  
Dermatomyositis  
Systemic sclerosis  
Mixed connective tissue disease

**Sarcoidosis**

**Drugs**

Cocaine  
Amphetamine  
Adrenaline/mimics

**Infections/immune complexes**

**Viral**

VZV, HIV

**Bacteria**

Syphilis, TB, Mycoplasma, Rickettsia

**Fungi**

Aspergillosis, Mucormycosis, Histoplasma  
Coccidioidomycosis, Candidosis

**Parasites**

Cysticercosis, Toxoplasma

**Secondary cryoglobulins, imm. complex**

Hep. C, Hep. B, CMV, EBV, parvovirus B19  
Lyme disease, Malaria

**Malignancy**

Hodgkin's and non-Hodgkin lymphomas  
Paraneoplasia  
Lymphomatoid granulomatosis  
Malignant angioendotheliomatosis

## TABLE TWO

Proposed criteria for the diagnosis of CNS vasculitis (CNSV)

### Definite

- *Clinical presentation suggestive of CNSV with exclusion of alternative possible diagnoses and of primary systemic vasculitic syndrome*
- PLUS the presence of positive CNS histology, i.e., biopsy or autopsy showing CNS angiitis (granulomatous, lymphocytic, or necrotizing), including evidence of vessel wall damage.

### Possible

- *Clinical presentation compatible CNSV with exclusion of alternative possible diagnoses and of primary systemic vasculitic syndrome*
- PLUS laboratory and imaging support for CNS inflammation (elevated levels of CSF - protein and/or cells, and/or the presence of oligoclonal bands and/or MRI evidence compatible with CNSV), with [contrast angiographic\[CR2\]](#)\* exclusion of other specific entities
- BUT without histological proof of vasculitis.

\*Certain disorders – perhaps most particularly moyamoya disease, [may](#) require formal contrast angiography for definitively diagnosis,<sup>57,58</sup> ~~hence our suggesting this rather than MRA or CTA~~

TABLE THREE

Conditions that may show 'vasculitic' changes on contrast angiography

Intracranial atherosclerosis	Subarachnoid hemorrhage
CADASIL	Intracerebral hematoma
Reversible Cerebral Vasoconstriction Syndrome	Migraine
Antiphospholipid syndrome	Sickle cell disease
Fibromuscular dysplasia	Alzheimer's disease
Intravascular lymphoma	Multiple cerebral emboli [e.g., SBE]
Herpes zoster arteritis	Marfans', Ehlers-Danlos syndromes
Vasospasm [e.g., drug-related]	Severe hypertension
Moyamoya disease and syndrome	Acute trauma
Radiation vasculopathy	

## REFERENCES

- 1 Lie, J. T. Primary (granulomatous) angiitis of the central nervous system: a clinicopathologic analysis of 15 new cases and a review of the literature. *Hum.Pathol.* **23**, 164-171 (1992).
- 2 Cravioto, F. & Feigin, I. Non-infectious granulomatous angiitis with a predilection for the nervous system. *Neurology* **9**, 599-609 (1959).
- 3 Scolding, N. J. *et al.* The recognition, diagnosis and management of cerebral vasculitis: a European survey. *Eur.J Neurol* **9**, 343-347 (2002).
- 4 Schmidley, J. W. in *Central Nervous System Angiitis* 1-28 (Butterworth Heinemann, 2000).
- 5 Younger, D. S., Hays, A. P., Brust, J. C. & Rowland, L. P. Granulomatous angiitis of the brain. An inflammatory reaction of diverse etiology. *Arch.Neurol.* **45**, 514-518 (1988).
- 6 Joseph, F. G. & Scolding, N. J. Cerebral Vasculitis - a practical approach. *Practical Neurology* **2**, 80-93 (2002).
- 7 Salvarani, C., Brown Jr, R. D. & Hunder, G. G. Adult primary central nervous system vasculitis. *The Lancet* **380**, 767-777 (2012).
- 8 Hajj-Ali, R. A. & Calabrese, L. H. Diagnosis and classification of central nervous system vasculitis. *J Autoimmun* **48-49**, 149-152, doi:10.1016/j.jaut.2014.01.007 (2014).
- 9 Calabrese, L. H. & Mallek, J. A. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine* **67**, 20-39 (1988).
- 10 Bhattacharyya, S. & Berkowitz, A. L. Primary angiitis of the central nervous system: avoiding misdiagnosis and missed diagnosis of a rare disease. *Pract Neurol* **16**, 195-200, doi:10.1136/practneurol-2015-001332 (2016).
- 11 Powers, W. J. Primary angiitis of the central nervous system: diagnostic criteria. *Neurol Clin* **33**, 515-526, doi:10.1016/j.ncl.2014.12.004 (2015).
- 12 Salvarani, C. *et al.* Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol.* **62**, 442-451 (2007).
- 13 de Boysson, H. *et al.* Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system. *Arthritis Rheumatol* **66**, 1315-1326, doi:10.1002/art.38340 (2014).
- 14 Abu, S. M. *et al.* Primary angiitis of the CNS diagnosed by angiography. *Q.J.Med.* **87**, 351-358 (1994).
- 15 Wang, L. J. *et al.* Study on the Clinical, Imaging, and Pathological Characteristics of 18 Cases with Primary Central Nervous System Vasculitis. *J Stroke Cerebrovasc Dis* **28**, 920-928, doi:10.1016/j.jstrokecerebrovasdis.2018.12.007 (2019).
- 16 Schuster, S. *et al.* Relapse rates and long-term outcome in primary angiitis of the central nervous system. *J Neurol* **266**, 1481-1489, doi:10.1007/s00415-019-09285-1 (2019).
- 17 Geri, G. *et al.* Central nervous system angiitis: a series of 31 patients. *Clin Rheumatol* **33**, 105-110, doi:10.1007/s10067-013-2403-3 (2014).
- 18 Vera-Lastra, O. *et al.* Primary and secondary central nervous system vasculitis: clinical manifestations, laboratory findings, neuroimaging, and treatment analysis. *Clin Rheumatol* **34**, 729-738, doi:10.1007/s10067-014-2831-8 (2015).
- 19 Kempster, P. A., McLean, C. A. & Phan, T. G. Ten year clinical experience with stroke and cerebral vasculitis. *J Clin Neurosci* **27**, 119-125, doi:10.1016/j.jocn.2015.08.042 (2016).
- 20 Birnbaum, J. & Hellmann, D. B. Primary angiitis of the central nervous system. *Arch Neurol* **66**, 704-709, doi:10.1001/archneurol.2009.76 (2009).
- 21 Moore, P. M. Central nervous system vasculitis. *Curr.Opin.Neurol.* **11**, 241-246 (1998).

- 22 Schmidley, J. W. (Butterworth Heinemann, 2000).
- 23 Scolding, N. J. in *Immunological and Inflammatory diseases of the central nervous system* (ed N. J. Scolding) 210-258 (Butterworth-Heinemann, 1999).
- 24 Scolding, N. J. *et al.* in *European Handbook of Neurological Management* Vol. 2nd (eds N. E. Gilhus, M. Barnes, & M. Brainin) 485-489 (Blackwell, 2011).
- 25 Hankey, G. Isolated angiitis/angiopathy of the CNS. Prospective diagnostic and therapeutic experience. *Cerebrovasc. Dis.* **1**, 2-15 (1991).
- 26 Scolding, N. J. *et al.* The syndrome of cerebral vasculitis: recognition, diagnosis and management. *Q.J.Med.* **90**, 61-73 (1997).
- 27 McVerry, F., McCluskey, G., McCarron, P., Muir, K. W. & McCarron, M. O. Diagnostic test results in primary CNS vasculitis: A systematic review of published cases. *Neurol Clin Pract* **7**, 256-265, doi:10.1212/CPJ.0000000000000359 (2017).
- 28 Eiden, S. *et al.* High-resolution contrast-enhanced vessel wall imaging in patients with suspected cerebral vasculitis: Prospective comparison of whole-brain 3D T1 SPACE versus 2D T1 black blood MRI at 3 Tesla. *PLoS one* **14**, e0213514, doi:10.1371/journal.pone.0213514 (2019).
- 29 Androudi, S. *et al.* Retinal vasculitis in rheumatic diseases: an unseen burden. *Clin Rheumatol* **32**, 7-13, doi:10.1007/s10067-012-2078-1 (2013).
- 30 de Boysson, H. *et al.* Concordance of Time-of-Flight MRA and Digital Subtraction Angiography in Adult Primary Central Nervous System Vasculitis. *AJNR. American journal of neuroradiology* **38**, 1917-1922, doi:10.3174/ajnr.A5300 (2017).
- 31 Chen, S. H. *et al.* Utility of diagnostic cerebral angiography in the management of suspected central nervous system vasculitis. *J Clin Neurosci* **64**, 98-100, doi:10.1016/j.jocn.2019.03.058 (2019).
- 32 Ferris, E. J. & Levine, H. L. Cerebral arteritis: classification. *Radiology* **109**, 327-341, doi:10.1148/109.2.327 (1973).
- 33 Alrawi, A., Trobe, J., Blaivas, M. & Musch, D. C. Brain biopsy in primary angiitis of the central nervous system. *Neurology* **53**, 858-860 (1999).
- 34 Koo, E. H. & Massey, E. W. Granulomatous angiitis of the central nervous system: Protean manifestations and response to treatment. *Journal of Neurology Neurosurgery and Psychiatry* **51**, 1126-1133 (1988).
- 35 Vollmer, T. L., Guarnaccia, J., Harrington, W., Pacia, S. V. & Petroff, O. A. C. Idiopathic granulomatous angiitis of the central nervous system: Diagnostic challenges. *Archives of Neurology* **50**, 925-930 (1993).
- 36 Duna, G. F. & Calabrese, L. H. Limitations of invasive modalities in the diagnosis of primary angiitis of the central nervous system. *J Rheumatol* **22**, 662-667 (1995).
- 37 Eleftheriou, D. *et al.* Investigation of childhood central nervous system vasculitis: magnetic resonance angiography versus catheter cerebral angiography. *Developmental medicine and child neurology* **52**, 863-867, doi:10.1111/j.1469-8749.2009.03591.x (2010).
- 38 Edgell, R. C. *et al.* The Role of Catheter Angiography in the Diagnosis of Central Nervous System Vasculitis. *Interventional neurology* **5**, 194-208, doi:10.1159/000445255 (2016).
- 39 Singhal, A. B. *et al.* Reversible cerebral vasoconstriction syndromes and primary angiitis of the central nervous system: clinical, imaging, and angiographic comparison. *Ann Neurol* **79**, 882-894, doi:10.1002/ana.24652 (2016).
- 40 Obusez, E. C. *et al.* High-resolution MRI vessel wall imaging: spatial and temporal patterns of reversible cerebral vasoconstriction syndrome and central nervous system vasculitis. *AJNR. American journal of neuroradiology* **35**, 1527-1532, doi:10.3174/ajnr.A3909 (2014).
- 41 Rice, C. M. *et al.* Brain biopsy in cryptogenic neurological disease. *Br.J Neurosurg* **25**, 614-620 (2011).

- 42 Hall, W. A. The safety and efficacy of stereotactic biopsy for intracranial lesions. *Cancer* **82**, 1749-1755 (1998).
- 43 Bai, H. X., Zou, Y., Lee, A. M., Lancaster, E. & Yang, L. Diagnostic Value and Safety of Brain Biopsy in Patients With Cryptogenic Neurological Disease: A Systematic Review and Meta-analysis of 831 Cases. *Neurosurgery* **77**, 283-295; discussion 295, doi:10.1227/NEU.0000000000000756 (2015).
- 44 Porretta, E. J., S.M.; Jordan, S.L.; Male, J.; Edwards, R.J.; Love, S; Scolding, N.J.; Rice, C.M. Safety and utility of brainstem biopsy and resection. *J Neurology Neurosurgery Psychiatry* **87**, e1 (2016).
- 45 Chu, C. T., Gray, L., Goldstein, L. B. & Hulette, C. M. Diagnosis of intracranial vasculitis: a multi-disciplinary approach. *J.Neuropathol.Exp.Neurol.* **57**, 30-38 (1998).
- 46 Dhawan, S., He, Y., Bartek, J., Jr., Alattar, A. A. & Chen, C. C. Comparison of Frame-Based Versus Frameless Intracranial Stereotactic Biopsy: Systematic Review and Meta-Analysis. *World Neurosurg*, doi:10.1016/j.wneu.2019.04.016 (2019).
- 47 Elbers, J., Halliday, W., Hawkins, C., Hutchinson, C. & Benseler, S. M. Brain biopsy in children with primary small-vessel central nervous system vasculitis. *Annals of Neurology* **68**, 602-610 (2010).
- 48 Rice, C. M. *et al.* Idiopathic hypereosinophilic syndrome: a new cause of vasculitis of the central nervous system. *J Neurol* **262**, 1354-1359, doi:10.1007/s00415-015-7720-9 (2015).
- 49 Scolding, N. J. *et al.* A{beta}-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain* **128**, 500-515 (2005).
- 50 Byram, K., Hajj-Ali, R. A. & Calabrese, L. CNS Vasculitis: an Approach to Differential Diagnosis and Management. *Curr Rheumatol Rep* **20**, 37, doi:10.1007/s11926-018-0747-z (2018).
- 51 de Boysson, H. *et al.* Maintenance therapy is associated with better long-term outcomes in adult patients with primary angiitis of the central nervous system. *Rheumatology (Oxford)* **56**, 1684-1693, doi:10.1093/rheumatology/kex047 (2017).
- 52 Hiemstra Tf, W. M. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled trial. *JAMA: The Journal of the American Medical Association* **304**, 2381-2388 (2010).
- 53 Salvarani, C. *et al.* Rituximab therapy for primary central nervous system vasculitis: A 6 patient experience and review of the literature. *Autoimmun Rev* **18**, 399-405, doi:10.1016/j.autrev.2018.12.002 (2019).
- 54 Lie, J. T. Biopsy diagnosis of systemic vasculitis. *Baillieres.Clin.Rheumatol.* **11**, 219-236 (1997).
- 55 Kadkhodayan, Y. *et al.* Primary angiitis of the central nervous system at conventional angiography. *Radiology* **233**, 878-882, doi:10.1148/radiol.2333031621 (2004).
- 56 Berlit, P. Primary angiitis of the CNS--an enigma that needs world-wide efforts to be solved. *Eur J Neurol* **16**, 10-11, doi:10.1111/j.1468-1331.2008.02348.x (2009).
- 57 Scott, R. M. & Smith, E. R. Moyamoya disease and moyamoya syndrome. *The New England journal of medicine* **360**, 1226-1237, doi:10.1056/NEJMra0804622 (2009).
- 58 Hasuo, K. *et al.* Moya moya disease: use of digital subtraction angiography in its diagnosis. *Radiology* **157**, 107-111, doi:10.1148/radiology.157.1.3898215 (1985).